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REMARKS

I. Status Summary

Claims 1-31 were filed with the subject application. Claims 1-8, 12-15, 18-24, and 31 were cancelled by Amendment C, filed March 1, 2006, pursuant to the Patent Office indication of allowance of claim 11. Accordingly, claim 11 is currently pending in the subject application and has been examined by the Patent Office.

The Patent Office has withdrawn the previous indication of allowability of claim 11.

Claim 11 has been rejected under the provisions of 35 U.S.C. §103(a) as allegedly being unpatentable over U.S. Patent Publication No. 2003/0077607 A1 to Jakobsen *et al.* (hereinafter referred to as "Jakobsen *et al.*"), and the journal article to Cregan, *et al.* (1999) *Theor Appl Genet* **98**: 919-928 (hereinafter referred to as "Cregan *et al.*"), and the publication to Sambrook *et al.*, Molecular Cloning: A laboratory Manual, New York: Cold Spring Harbor Laboratory, January 15, 2001, Vol. 2, pages 11.35 and 11.98-11.106 (hereinafter referred to as "Sambrook *et al.*"), and the publication to Brown (1999) Genomes, New York: John Wiley & Sons, Inc, 1999, pages 18-23 and 136-137 (hereinafter referred to as "Brown"), and the publication to Liu *et al.* (1996) *Theor Appl Genet* **93**:869-876 (hereinafter referred to as "Liu *et al.*").

Claims 32-51 have been added herein. Support for new claims 32-51 can be found throughout the specification as filed, including particularly in claims 1-8, 12-15, 18-24 and 32, previously cancelled in response to the Patent Office's indication of allowance of claim 11. No new matter has been added.

Reconsideration of the subject application in view of the amendments and remarks set forth herein is respectfully requested.

II. Response to the 35 U.S.C. §103(a) Rejection of Claim 11 over Jakobsen *et al.* and Cregan *et al.* and Sambrook *et al.* and Brown and Liu *et al.*

The Patent Office asserts that Jakobsen *et al.* teaches or suggests all the elements of rejected claim 11, except the use of "simple sequence repeat" (SSR) target molecules, as recited in claim 11. The Examiner further admits Jakobsen *et al.*

fails to teach the use of simple sequence repeat target molecules, and the use of a SSR portion of the hybridized duplex is a portion of an insert in a 3.5 kb clone. However, the Examiner argues that the combined references of Cregan *et al.*, Sambrook *et al.*, Brown, teach the use of SSRs as target molecules. The Examiner further asserts that the combined references Cregan *et al.*, Sambrook *et al.*, Brown and Liu *et al.* teach the use of an SSR portion comprising 1, 2, 3, or 4 base repeats, as well as the use of a 3.5 kb clone. Further, the Examiner asserts that the combined references Cregan *et al.*, Sambrook *et al.*, Brown and Liu *et al.* teach that the plasmid clones can be used to produce clones of SSRs.

Accordingly, the Patent Office asserts that it would have been obvious to one of ordinary skill in the related art at the time the invention was made to capture SSRs as taught by the combined Cregan *et al.*, Sambrook *et al.*, Liu *et al.*, and Brown references using LNAs as taught by Jakobsen *et al.*

After careful review of the instant rejection and the Patent Office's basis therefore, applicants respectfully traverse the rejection and submit the following remarks.

In response to the above-discussed rejection of claim 11 based on 35 U.S.C. § 103(a), applicants respectfully submit the attached Declaration under 37 CFR § 1.131 as Exhibit A. Summarily, the attached Declaration establishes that the inventive subject matter of the currently pending claims was invented prior to the earliest effective priority date of Jakobsen *et al.*, which is March 25, 2001. Consequently, it is respectfully submitted that Jakobsen *et al.* cannot properly be relied upon as a prior art reference against claim 11.

The Examiner first contended in the final Official Action mailed April 7, 2005 that the 37 C.F.R. § 1.131 Declaration submitted November 17, 2004 with Amendment A was defective. In response, applicants submitted a replacement 37 C.F.R. § 1.131 Declaration with Amendment B, filed October 7, 2005. In an Advisory Action dated November 29, 2005, the Patent Office refused to accept the 37 C.F.R. § 1.131 Declaration submitted with Amendment B, presumably because the patent application was under final rejection. Accordingly, applicants resubmit herewith the 37 C.F.R. § 1.131 Declaration originally filed with Amendment B. Applicants maintain

that the 37 C.F.R. § 1.131 Declaration addresses all of the Patent Office's assertions of defectiveness, and is not presented in response to a final rejection.

Specifically, applicants respectfully submit that the 37 C.F.R. § 1.131 Declaration includes signatures from both inventors and precisely provides explanation as to proof of acts amounting to conception, diligence and reduction to practice. For example, applicants point to the statements presented within the Declaration, as well as the data provided in Exhibits A and B. The Declaration also states that the inventive activity occurred in the United States.

Further, the Declaration sets forth additional facts and/or evidence to corroborate completion of the invention before the particular date. To elaborate, the data set forth on the first page of Exhibit A of the Declaration is a reproduction of p. 146 of a notebook entry entitled "New LNA Oligos," which records experimental conditions related to capturing specific target nucleotide sequences utilizing locked nucleic acids (LNAs) and further including characterizations of the LNAs and reagent quantities and conditions used in the experiments. Specifically, the first page of Exhibit A describes one or more modified oligonucleotide conjugates comprising at least one LNA and a linking molecule. The modified oligonucleotide referred to as "Torrey-2" comprises the listed sequence of $(GC)_6$, with the LNA residues are shown in bold. The linking molecule used for Torrey-2 was biotin.

The second page of Exhibit A is a reproduction of p. 147 of a notebook entry entitled "LNA Capture That Worked," which records further experimental conditions and reagents related to capturing specific target nucleotide sequences utilizing LNAs and results of an experiment. The second page of Exhibit A describes incubating a sample of nucleic acids with the LNA conjugate to thereby form one or more hybridized duplexes, wherein each duplex comprises a target simple sequence repeat ("SSR") portion and an LNA conjugate. The specific experimental conditions labeled "CN" and notated with a box are labeled as "WORKED." This comment is indicative of the successful capture of specific target nucleotide sequences utilizing an LNA, as recited in the pending claims. Particularly, the boxed data on page 147 indicates that 2.5μl of tomato library DNA was incubated with Torrey-2 LNA conjugate and Buffer C to form a hybridized duplex.

Further, the third page of Exhibit A is a reproduction of p. 150 of a notebook entry entitled "LNA Capture Protocol" and describes the protocol used to acquire the dates set forth on the other pages, wherein hybridized duplexes are contacted with a linking source so that the linking molecule forms a bond with the linking source. Specifically, the protocol recites that the biotinylated LNAs are contacted with streptavidin-coated magnetic beads and incubated to allow the biotin to form a bond with the streptavidin-coated beads. The protocol further recites that the hybridized duplexes are then separated from the sample of nucleic acids by extracting the linking source from the sample, followed by a washing step and an incubating step so that the target SSRs dissociate from the LNA conjugates and the magnetic beads. Specifically, the protocol recites that the magnetic beads are separated from the sample of nucleic acids by use of a magnet, the beads washed eight times in Buffer C, and incubated in Buffer E in order to separate the SSRs from the beads. (This step is also recited on page 147 of the laboratory notebook provided on the second page of Exhibit A: "90°C in 150µl Buffer E – 20 min."). Next, the protocol recites that the SSRs are ethanol precipitated overnight, and purified using a PCR purification kit. Finally, the protocol recites that Life Technologies DH12S cells were transformed with the captured SSR DNA, grown overnight, the colonies picked, and stored at a temperature of -80°C for sequencing.

Further, Exhibit B is a true and accurate reproduction of the results of sequence data chromatographs resulting from the experiments discussed above and provide in Exhibit A. Page 147 of the laboratory notebook provided in the second page of Exhibit A recites that the experiment worked, and points to plate T2NC01. The sequence data of Exhibit B verifies that the SSRs were recovered and that the experiment was successful. For example, wells E04 and F09 of plate T2NC01 were sequenced and the SSR $(CA)_6$ was discovered at bases 221-232 and 131-142, respectively. This particular sequence data is provided herein in Exhibit B, and the SSRs are underlined for clarity.

Applicants respectfully submit that the Declaration and data provided in Exhibits A and B are commensurate in scope with the pending claims. Under MPEP § 715.03, a cited reference applied against generic claims may be antedated by a

declaration under 37 C.F.R. § 1.131 showing completion of the invention of only a single species within the genus prior to the effective date of the reference. Further, even assuming *arguendo* the data provided in the present Declaration is insufficient to support the entire claimed genus, a 37 C.F.R. § 131 declaration need only show prior invention of so much of the claimed subject matter as is disclosed by the reference. *In re Stempel,* 241 F. 2d 755, 113 U.S.P.Q. 77 (C.C.P.A 1957).

In Stempel, the court held that a declaration provided properly antedated the reference, stating: "...all the applicant can be required to show is priority with respect to so much of the claimed invention as the reference happens to show. When he has done that he has disposed of the reference." *Id.* at 759-60, 113 U.S.P.Q. at 81; see also *In re* Stryher, 435 F. 2d 1340, 1341, 168 U.S.P.Q. 372, 373 (C.C.P.A. 1971) (applying the principle that a Declaration under 37 C.F.R. § 131 need only show prior invention of as much as taught by the reference).

Thus, applicants respectfully submit that a non-defective, properly submitted Declaration under 37 C.F.R. § 131 has been submitted and is believed to address the Jakobsen *et al.* reference.

In the instant rejection, the Patent Office relies upon Jakobsen *et al.* as a reference to teach using modified LNAs for the capture of nucleic acids. Applicants respectfully submit that none of the remaining references Cregan *et al.*, Sambrook *et al.*, Brown, and/or Liu *et al.* teach, alone or in combination, the use of LNAs for the capture of target SSRs. As such, applicants respectfully submit none of the remaining references cited by the Patent Office specifically teach or suggest all the claim limitations of claim 11, and therefore claim 11 is believed to be patentably distinguished over the cited references, either alone or in combination.

Applicants therefore respectfully request that the 35 U.S.C. §103(a) rejection of claim 11 based Jakobsen *et al.* and Cregan *et al.* and Sambrook *et al.* and Brown and Liu *et al.* be withdrawn at this time. Allowance of claim 11 is also respectfully requested.

III. Discussion of New Claims 32-51

New claims 32-51 have been added herein as indicated above.

New claim 32 recites an *in vitro* method of capturing one or more target simple sequence repeats, the method comprising the steps of providing one or more modified oligonucleotide conjugates, wherein each of the modified oligonucleotide conjugates comprises at least one locked nucleic acid and a linking molecule; incubating a sample of nucleic acids with the modified oligonucleotide conjugates, thereby forming one or more hybridized duplexes, wherein each duplex comprises a target simple sequence repeat portion and a modified oligonucleotide conjugate portion; contacting substantially all of the hybridized duplexes with a linking source, such that the linking molecule of each duplex that contacts the linking source forms a bond with the linking source; and separating substantially all of the hybridized duplexes from the sample of nucleic acids by extracting the linking source from the sample. Applicants respectfully submit that new claim 32 is substantially identical to original claim 1, previously cancelled in response to the Patent Office's now withdrawn indication of allowance of claim 11. Accordingly, support for new claim 32 can be found throughout the specification as filed, including particularly in original claim 1. No new matter has been added.

New claim 33 depends from claim 32 and recites that the sample of nucleic acids contains one or more nucleic acid molecules having a nucleotide sequence which comprises one or more target simple sequence repeats. Applicants respectfully submit that new claim 33 is substantially identical to original claim 2, previously cancelled in response to the Patent Office's now withdrawn indication of allowance of claim 11. Accordingly, support for new claim 33 can be found throughout the specification as filed, including particularly in original claim 2. No new matter has been added.

New claim 34 depends from claim 32 and recites that the captured simple sequence repeat portion comprises 1, 2, 3, or 4 base repeats. Applicants respectfully submit that new claim 34 is substantially identical to original claim 3, previously cancelled in response to the Patent Office's now withdrawn indication of allowance of claim 11. Accordingly, support for new claim 34 can be found throughout the

specification as filed, including particularly in original claim 3. No new matter has been added.

New claim 35 depends from claim 32 and recites the step of disassociating the targeted simple sequence repeat portion of each of the hybridized duplexes from the linking source and modified oligonucleotide conjugate. Applicants respectfully submit that new claim 35 is substantially identical to original claim 4, previously cancelled in response to the Patent Office's now withdrawn indication of allowance of claim 11. Accordingly, support for new claim 35 can be found throughout the specification as filed, including particularly in original claim 4. No new matter has been added.

New claim 36 depends from claim 35 and recites that the disassociating step further comprises incubating the hybridized duplexes with an alkaline buffer, such that the targeted simple sequence repeat portion is disassociated from the modified oligonucleotide conjugate and the linking source. Applicants respectfully submit that new claim 36 is substantially identical to original claim 5, previously cancelled in response to the Patent Office's now withdrawn indication of allowance of claim 11. Accordingly, support for new claim 36 can be found throughout the specification as filed, including particularly in original claim 5. No new matter has been added.

New claim 37 depends from claim 36 and recites that the alkaline buffer has a pH between 9 and 10. Applicants respectfully submit that new claim 37 is substantially identical to original claim 6, previously cancelled in response to the Patent Office's now withdrawn indication of allowance of claim 11. Accordingly, support for new claim 37 can be found throughout the specification as filed, including particularly in original claim 6. No new matter has been added.

New claim 38 depends from claim 32 and recites that the incubating step comprises using reaction conditions at which substantially all of the targeted simple sequence repeats form a strand displacing "A" helix with the modified oligonucleotide conjugates. Applicants respectfully submit that new claim 38 is substantially identical to original claim 7, previously cancelled in response to the Patent Office's now withdrawn indication of allowance of claim 11. Accordingly, support for new claim 38 can be found throughout the specification as filed, including particularly in original claim 7. No new matter has been added.

New claim 39 depends from claim 32 and recites that the method forms a new library enriched in the targeted simple sequence repeat or repeats. Applicants respectfully submit that new claim 39 is substantially identical to original claim 8, previously cancelled in response to the Patent Office's now withdrawn indication of allowance of claim 11. Accordingly, support for new claim 39 can be found throughout the specification as filed, including particularly in original claim 8. No new matter has been added.

New claim 40 depends from claim 32 and recites the step of obtaining the sample of simple sequence repeats from a plasmid library. Applicants respectfully submit that new claim 40 is substantially identical to original claim 12, previously cancelled in response to the Patent Office's now withdrawn indication of allowance of claim 11. Accordingly, support for new claim 32 can be found throughout the specification as filed, including particularly in original claim 12. No new matter has been added.

New claim 41 depends from claim 40 and recites that at least one of the one or more plasmids is a circular plasmid. Applicants respectfully submit that new claim 41 is substantially identical to original claim 13, previously cancelled in response to the Patent Office's now withdrawn indication of allowance of claim 11. Accordingly, support for new claim 41 can be found throughout the specification as filed, including particularly in original claim 13. No new matter has been added.

New claim 42 depends from claim 32 and recites the step of obtaining the sample of simple sequence repeats from a double stranded DNA plasmid library. Applicants respectfully submit that new claim 42 is substantially identical to original claim 14, previously cancelled in response to the Patent Office's now withdrawn indication of allowance of claim 11. Accordingly, support for new claim 42 can be found throughout the specification as filed, including particularly in original claim 14. No new matter has been added.

New claim 43 depends from claim 32 and recites the step of obtaining the sample of simple sequence repeats from DNA sequences. Applicants respectfully submit that new claim 43 is substantially identical to original claim 15, previously cancelled in response to the Patent Office's now withdrawn indication of allowance of

claim 11. Accordingly, support for new claim 43 can be found throughout the specification as filed, including particularly in original claim 15. No new matter has been added.

New claim 44 depends from claim 32 and recites that the modified oligonucleotides comprise nucleotide sequences that are complementary to the target simple sequence repeats. Applicants respectfully submit that new claim 44 is substantially identical to original claim 18, previously cancelled in response to the Patent Office's now withdrawn indication of allowance of claim 11. Accordingly, support for new claim 44 can be found throughout the specification as filed, including particularly in original claim 18. No new matter has been added.

New claim 45 depends from claim 32 and recites that the linking molecule comprises biotin bound to a 5' end of the modified oligonucleotide. Applicants respectfully submit that new claim 45 is substantially identical to original claim 19, previously cancelled in response to the Patent Office's now withdrawn indication of allowance of claim 11. Accordingly, support for new claim 45 can be found throughout the specification as filed, including particularly in original claim 19. No new matter has been added.

New claim 46 depends from claim 32 and recites that the linking molecule comprises an antibody, biotin, immunoglobulin, or carbohydrate. Applicants respectfully submit that new claim 46 is substantially identical to original claim 20, previously cancelled in response to the Patent Office's now withdrawn indication of allowance of claim 11. Accordingly, support for new claim 46 can be found throughout the specification as filed, including particularly in original claim 20. No new matter has been added.

New claim 47 depends from claim 32 and recites that the linking source comprises streptavidin-coated beads. Applicants respectfully submit that new claim 47 is substantially identical to original claim 21, previously cancelled in response to the Patent Office's now withdrawn indication of allowance of claim 11. Accordingly, support for new claim 47 can be found throughout the specification as filed, including particularly in original claim 21. No new matter has been added.

New claim 48 depends from claim 32 and recites that the linking source comprises an antigen, streptavidin, protein A, or lectin. Applicants respectfully submit that new claim 48 is substantially identical to previously presented claim 22, previously cancelled in response to the Patent Office's now withdrawn indication of allowance of claim 11. Accordingly, support for new claim 48 can be found throughout the specification as filed, including particularly in previously presented claim 22. No new matter has been added.

New claim 49 depends from claim 32 and recites that the separating step comprises using a magnet to extract the linking source and hybridized duplexes from the sample of simple sequence repeats. Applicants respectfully submit that new claim 49 is substantially identical to original claim 23, previously cancelled in response to the Patent Office's now withdrawn indication of allowance of claim 11. Accordingly, support for new claim 49 can be found throughout the specification as filed, including particularly in original claim 23. No new matter has been added.

New claim 50 recites an *in vitro* method of capturing one or more target simple sequence repeats, the method comprising the steps of providing one or more modified oligonucleotide conjugates, wherein each of the modified oligonucleotide conjugates comprises at least one locked nucleic acid and a linking molecule biotin; incubating a sample of nucleic acids with the modified oligonucleotide conjugates, thereby forming one or more hybridized duplexes, wherein each duplex comprises a target simple sequence repeat portion and a modified oligonucleotide conjugate portion; binding the linking molecule biotin on the modified oligonucleotide conjugates to streptavidin on coated magnetic beads, such that the magnetic beads are linked to the hybridization duplexes; separating the hybridized duplexes from the other materials with a magnet; washing the hybridized duplexes; incubating the hybridized duplexes with buffer of pH of about 9.5 such that the targeted simple sequence repeat dissociates from the modified oligonucleotide conjugate and the magnetic bead; transforming the simple sequence repeats in E coli; and sequencing the transformed simple sequence repeats. Applicants respectfully submit that new claim 50 is substantially identical to previously presented claim 24, deleted in Amendment C, filed March 1, 2006, in response to the Patent Office's now withdrawn indication of

allowance of claim 11. Accordingly, support for new claim 50 can be found throughout the specification as filed, including particularly in original claim 24. No new matter has been added.

New claim 51 depends from claim 50 and recites that the target simple sequence repeat is 5'-$(CA)_6$-3', wherein the modified oligonucleotide conjugate comprises 3 biotinylated $(GT)_6$-5' bicyclic structures, wherein the LNAs occur on at least the first G, and wherein the target source is a plasmid library. Applicants respectfully submit that new claim 51 is substantially identical to previously presented claim 31, deleted in Amendment C, filed March 1, 2006, in response to the Patent Office's now withdrawn indication of allowance of claim 11. Accordingly, support for new claim 51 can be found throughout the specification as filed, including particularly in previously presented claim 31. No new matter has been added.

Accordingly, applicants submit that new claims 32-51 correspond to original claims. Particularly, claims 32-39 correspond to original claims 1-8, respectively; claims 40-43 correspond to original claims 12-15, respectively; claims 44-50 correspond to claims 18-24, respectively; and claim 50 corresponds to claim 24. Accordingly, applicants respectfully submit that all of new claims 32-51 are readable upon the elected species in accordance with M.P.E.P. §809.02(a).

Particularly, applicants respectfully submit that new claims 32-51 are readable on the elected species set forth in the October 20, 2003 Response to the Restriction Requirement, set forth as follows:

Subgroup I – species of target simple sequence repeat: 5'-$(CA)_6$-3'

Subgroup II – species of modified oligonucleotide conjugate: 3 biotinylated (GT)6-5'-bicyclic structure; LNA occurs first G

Subgroup III – species of linking molecule: biotin

Subgroup IV – species of linking source: streptavidin

Subgroup V – species of separation: magnetic bead separation

Subgroup VI – species of disassociation: alkaline buffer, pH about 9.5

Subgroup VII – species of target source: plasmid library.

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VI. Conclusion

In light of the above amendments and remarks, it is respectfully submitted that the present application is now in proper condition for allowance, and such action is earnestly solicited.

If any minor issues should remain outstanding after the Examiner has had an opportunity to study the Amendment and Remarks, it is respectfully requested that the Examiner telephone the undersigned attorney so that all such matters may be resolved and the application placed in condition for allowance without the necessity for another Action and/or Amendment.

DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge any other fee associated with the filing of this correspondence, to Deposit Account No. **50-0426**.

Respectfully submitted,

JENKINS, WILSON, TAYLOR, & HUNT, P.A.

Date: February 16, 2007 By: 

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